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Original Article

Resuscitation goals in septic shock: fluid therapy and vasoactive drugs, an integrative review

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Abstract

Severe sepsis and septic shock are complex syndromes with high mortality that frequently affect ICU patients. Contributions such as the Surviving Sepsis campaign have led to the issuing of guidelines for managing these patients. This manuscript aims to provide a review of state of the art using a systematic review of resuscitation and the use of vasopressors in patients with septic shock. Using MESH terms and Boolean operators, systematic research for information was carried out in PubMed in February 2023. We included 28 articles of which 18 were selected using the prism algorithm that met the inclusion criteria (analysis of septic shock, fluid resuscitation, or the use of vasopressors in septic shock in humans). In conclusion, the management of septic shock should be performed based on clear objectives to improve outcomes, for which maintenance of physiological levels of oxygenation, serum lactate, and mean arterial blood pressure are crucial.

Keywords: Resuscitation, fluid therapy, vasoconstrictors agents, sepsis, septic shock

Introduction

Shock is a life-threatening condition characterized by inadequate oxygen (O2) delivery to tissues (De Backer et al, 2022). Sepsis is a life-threatening organ dysfunction caused by dysregulation of the host's immune response to infection (Evans et al, 2021). Severe sepsis is the appearance of organic dysfunction induced by sepsis or tissue hypoperfusion resulting from progressive systemic inflammation and a procoagulant response caused by infectious processes due to inflammatory mediators and thrombin procoagulant (which acts reciprocally) leading to the appearance of diffuse endovascular lesions and organ dysfunction (Bone et al, 1997; Bernard et al 2001; Martin, 2021). Septic shock is the combination of hemodynamic, circulatory, and metabolic-cellular alterations, triggered by the progression of sepsis to severe sepsis, accompanied by shock (persistence of elevated serum lactate, with or without hypotension) (del Río-Carbajo et al, 2022). Sepsis and septic shock are associated with a high incidence and mortality (Lombo Moreno, 2021; Andaluz-Ojeda et al, 2021).

Similar reviews have been conducted previously, such as Simpson et al. (2017), which initiated the previously mentioned setting of resuscitation goals for patients with septic shock, especially within the first hour or Sharawy et al. (2015) to establish progress in the management of patients with sepsis. Over the last 19 years, updates on the management of patients affected by sepsis and septic shock have been presented through the publication of studies and updates such as the Surviving Sepsis Campaign (Evans et al, 2021). The objective of the present investigation is to describe the state of the art in the management of resuscitation for goals in septic shock.

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Methods

For the preparation of the manuscript and presentation, the context of septic shock was considered (this being the most frequent type of shock). For the selection of documents, a systematic search of the information was carried out using the terms MESH and Boolean operators (AND and NOT) in the Pubmed database, IN the following order (resuscitation) AND (Shock) AND (Fluid therapy) AND (Vasoconstrictor Agents)) AND (Sepsis) AND (Shock, Septic) NOT (Shock, Cardiogenic) NOT (Shock, Hemorrhagic) NOT (Shock, Surgical)) NOT (Shock, Traumatic), applying the text availability (free full text) and publication date (5 years) filters.

For the elaboration of the discussion, the analysis-synthesis method was used, cataloging the retrieved articles, excluding the following types: comments, case reports, conference reports, panels of experts, opinion articles, positions, animal tests, research protocols, and articles that did not explore management or resuscitation with fluids and vasopressors in septic shock, as detailed in Figure 1.

Results

Twenty-eight articles were obtained, of which 18 that met the inclusion criteria were selected using the PRISMA algorithm (analyzing septic shock, fluid resuscitation, or the use of vasopressors in septic shock in humans) (**Figure 1**). **Table 1** describes the type of research or article retrieved from the PubMed search, by year of publication and its title (n=18).

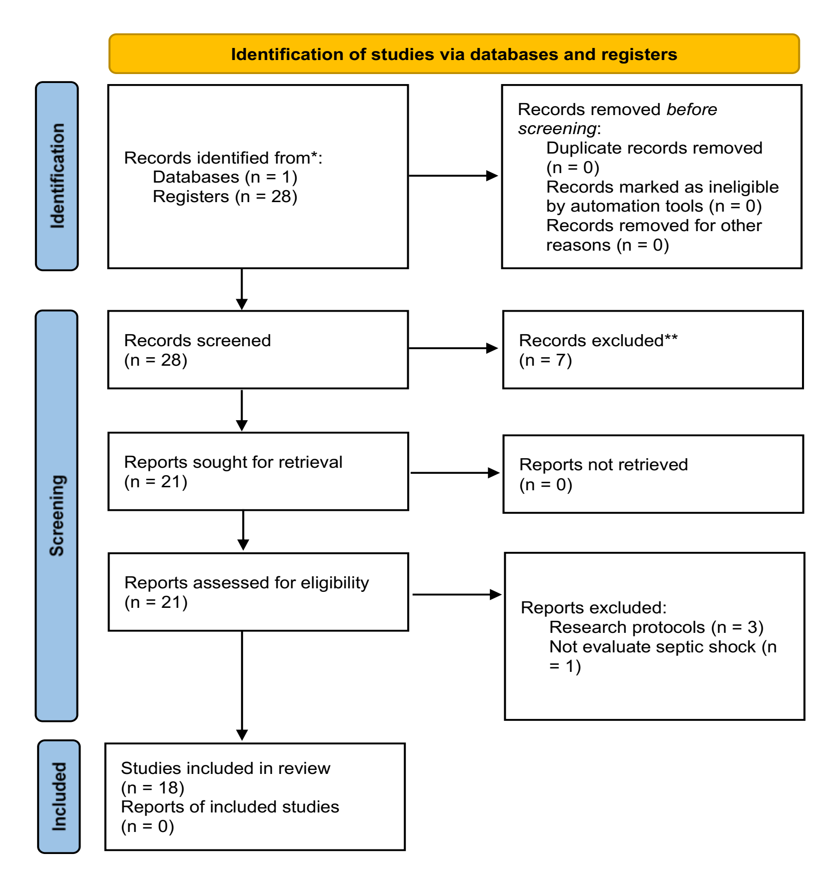


Figure 1. PRISMA algorithm showing the selection of articles or publications included for analysis-synthesis. Elaborated by the authors.

Table 1. Studies retrieved from PubMed search. Elaborated by the authors.

Study design	Publication year	Title	Reference
Prospective multicentre study	2018	Prognosis of patients excluded by the definition of septic shock based on their lactate levels after initial fluid resuscitation: a prospective multi-center observational study	Ko et al, 2018
Prospective cohort study	2018	Effects of Hydrocortisone on Regulating Inflammation, Hemodynamic Stability, and Preventing Shock in Severe Sepsis Patients	Zhao & Ding, (2018)Menezes et al, (2018)
Non-randomized study	2018	Perfusion index for assessing microvascular reactivity in septic shock after fluid resuscitation	Menezes et al, (2018)
Randomized clinical trial	2019	Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients with Septic Shock	Hernandez et al, (2019)
Non-randomized study	2019	Cardiovascular determinants of resuscitation from sepsis and septic shock	Guarracino et al, (2019)
Non-randomized retrospective observational study.	2019	Central venous pressure value can assist in adjusting norepinephrine dosage after the initial resuscitation of septic shock	Dong-Kai and Wei (2019)
Non-randomized retrospective observational study.	2019	The mottling score is a strong predictor of 14day mortality in septic patients whatever vasopressor doses and other tissue perfusion parameters	Dumas et al, (2019)
Prospective, multicentre, randomized, parallel-group, prospective trial.	2020	Systematic assessment of fluid responsiveness during early septic shock resuscitation: secondary analysis of the ANDROMEDA-SHOCK trial	Kattan et al, (2020)
Non-randomized study	2020	Effects of a very early start of norepinephrine in patients with septic shock: a propensity score-based analysis	Ospina et al, (2020)
Randomized clinical trial	2020	Fluid Response Evaluation in Sepsis Hypotension and Shock	Douglas et al, (2020)
Retrospective Cohort Study	2021	Sepsis in two hospitals in Rwanda: A retrospective cohort study of presentation, management, outcomes, and predictors of mortality	Hopkinson et al, (2021)
Prospective cohort study	2021	Left ventricular-arterial coupling as a predictor of stroke volume response to norepinephrine in septic shock – a prospective cohort study	Zhou et al, (2021)
Prospective secondary analysis	2021	Right Ventricular Dysfunction in Early Sepsis and Septic Shock	Lanspa et al, (2021)
Retrospective study	2021	Predictive value of change in effective arterial elastance in norepinephrine weaning: a retrospective study	Yang et al, (2021)
Review	2021	Management of sepsis and septic shock in the emergency department	Gavelli et al, (2021)
Review	2021	Sepsis With Preexisting Heart Failure: Management of Confounding Clinical Features	Jones et al, (2021)
Single-centre randomized clinical trial	2022	Effect of methylene blue on hemodynamic and metabolic response in septic shock patients	Luis-Silva et al, (2022)
Review	2022	A plea for personalization of the hemodynamic management of septic shock	De Backer et al, (2022)

Ko et al. (2018) compared the clinical outcomes of the group of patients excluded from the new definition of septic shock (the excluded group, defined by a baseline lactate level ≥2 mmol/L; subsequent lactate level <2 mmol/L) with the group with septic shock definition SEPSIS-3 (defined by a subsequent lactate level ≥2 mmol/L regardless of the initial lactate level) in which they observed that 28-day mortality was significantly lower in the excluded group than in the group with the SEPSIS-3 definition of septic shock (8.2% compared to 26.4%), in-hospital mortality also being

lower in the excluded group compared to the SEPSIS-3 definition group (12.2% *vs*. 30.1%), demonstrating that excluding patient by lactate levels after fluid resuscitation may be reasonable, given the low 28-day mortality observed in these patients (Ko et al, 2018).

Menezes et al. (2018) observed that reactive hyperemia in patients with septic shock, when evaluated with the perfusion index, seems to be altered only in the initial phase of the post-ischemic response and remains considerably preserved in the last phase, despite severe vascular damage from sepsis.

Zhao and Ding (2018) measured the levels of inflammatory cytokines in patients with the definition of severe sepsis during treatment to explore the mechanisms by which hydrocortisone benefits patients with severe sepsis, noting that at the beginning the patients treated with hydrocortisone presented elevated levels of proinflammatory cytokines, and after treatment with it, a decrease in serum cytokines was found, however, the cytokine levels of patients not treated with hydrocortisone remained relatively stable or decreased with over time gradually, clarifying that the sample limit might not be sufficient to control for confounding factors between groups.

Hernandez et al. (2019) described the results of a randomized study of 28-day mortality in patients with septic shock, comparing the strategy of directed peripheral perfusion (capillary refill) vs. the strategy directed by the level of serum lactate directed in resuscitation, noting that peripheral perfusion-directed resuscitation was associated with beneficial effects on the SOFA score secondary outcome at 72 hours and lower 28-day mortality in the predefined subgroup of patients with less severe organ dysfunction at baseline, however, no reduction in mortality was observed when compared with the strategy directed by serum lactate levels.

Guarracino et al. (2019) analyzed the response of cardiovascular status to resuscitation according to the definition of surviving sepsis (DSS) utilizing the cardiac index (CI) after initial volume expansion (VE) within the first 3 hours with crystalloids at 30 ml/kg (in which the mean arterial pressure (MAP) rise >65 mmHg was observed) vs. norepinephrine (NE) of 0.01-1 mcg/kg/min with or without dobutamine (DB) 0.01 -1 mcg/kg/min or DB 5-15 mcg/kg/min.

It was observed that, of the 55 patients, 35 responded to IVS, and 20 required the use of NE due to sustained hypotension, increasing the MAT in 12 patients and slightly reducing it in 8. DB was administered to 6 of the 8 patients whose MAT remained hypotensive after NE and EV. Mortality was 47% at 30 days, concluding that initial DSS-based fluid resuscitation restores MAT and CI in most patients while restoring ventricular-arterial coupling (AVA) and left ventricular ejection fraction (LVEF), which together with other hemodynamic parameters are useful for predicting therapy and understanding differences in hemodynamic responses in patients with septic shock during resuscitation (Guarracino et al, 2019).

Dong-Kai and Wei (2019) have shown that in both the NE dose increase and decrease groups, the level of central venous pressure was negatively correlated with lactate clearance in septic shock, whereas the difference between the usual mean arterial pressure acquired from previous medical records and the mean arterial pressure (dMAP) was positively correlated with lactate clearance in septic shock.

Dumas et al. (2019) noted the high prognostic value of the Mottling Score in the legs for 14-day mortality in septic patients, regardless of vasopressor dose and other perfusion parameters, concluding that the decrease in the Mottling Score within the first 6h of resuscitation was significantly associated with a better outcome after SOFA adjustment.

Kattan et al. (2020) performed a post hoc analysis of the ANDROMEDA-SHOCK study database, which compared the effect of peripheral perfusion versus lactate-directed resuscitation on 28-day mortality. It was concluded that in patients with a negative response to fluid volumes, boluses can be interrupted without this having a negative impact, suggesting that the response to these can safely guide the resuscitation of a patient with septic shock.

Ospina et al. (2020), in their analysis of the effects of the very early use of norepinephrine in a total of 93 ICU cases vs. the delayed-onset vasopressor group; the former received fewer resuscitation fluids at the start of the vasopressor (0-510 ml) and during the first 8 hours (500-1900 ml [1100]), without this being associated with acute kidney injury or renal replacement therapy, while which was associated with a significant reduction in net fluid balance, as well as a reduced risk of 28-day mortality [HR 0.31, 95% CI 0.17–0.57].

Douglas et al. (2020), in their multicenter randomized trial, evaluated the efficacy of dynamic measures to guide the administration of fluids and vasopressors in patients with hypotension and shock associated with sepsis. The passive leg elevation (PLE)-guided resuscitation strategy resulted in significantly lower net fluid balance (1.37 L) and reduced renal and respiratory dysfunction (17.7% required mechanical ventilation) at 72 hours.

Hopkinson et al. (2021), in a retrospective cohort study in two hospitals in Rwanda, analyzed 111 cases of sepsis and 70 of septic shock (38.7%), where 92.7% received intravenous fluid therapy at a mean of 1.0 L in 8 hours, while that 94% received antimicrobials; 32% received vasopressors, and 46.4% required mechanical ventilation, the most frequent complication being acute kidney injury (19.3%), followed by acute respiratory distress syndrome (ARDS, 9.9%), acute liver injury or liver failure (1.1 %)), coagulopathies (0.6%), associating in the univariate analysis resuscitation with fluids with high volumes in the first eight hours (>2-3.5 L), management in intensive care, lack of reporting of diuresis, reception of vasopressors, mechanical ventilation by intubation, use of metronidazole or cefotaxime, steroids, exploratory laparotomies and insertion of central venous catheters, with higher mortality (31.5% in patients with sepsis and 82.9% in patients with septic shock).

Zhou et al. (2021), in a prospective cohort study conducted in an intensive care unit of a tertiary university hospital in China, evaluated whether left AVA could predict stroke volume (SV) response to NE in patients with shock. septic, measured by the relationship between arterial elastance (Ea) and left ventricular end-systolic elastance (Ees); noting that 56% (responders) before infusion with NE had a lower Ees and a higher Ea/Ees ratio than non-responders. NE significantly increased Ea and Ees in both groups, however, the Ea/Ees ratio normalized only in responders.

Lanspa et al. (2021) studied 393 patients with severe sepsis and septic shock, with left (LV) or right (RV) ventricular dysfunction (48% and 68% respectively) employing transthoracic ultrasound (TTE), excluding patients with TTE > 24 hours after the onset of sepsis or with poor image quality, of which 38% received vasopressors and 26% were on mechanical ventilation. They observed a 38% RV fractional area change and a TAPSE 1.8 cm (mean 0.6), despite holding an ejection fraction greater than 60%, the LV fractional change was -17% on average, also finding an index of abnormal myocardial performance frequently with a mean of 0.64, the normal being <0.5; the combination of LV diastolic (47%) and systolic (63%) dysfunction was observed in 286 cases (74%) of 385 patients, while RV dysfunction was observed in 48%. Of the cases presenting with some form of LV dysfunction, there was considerable overlap between RV and LV dysfunction (9%). RV dysfunction (alone or combined) was associated with higher mortality (31%) compared to those without it (16%), as well as fewer days free of mechanical ventilation or organ failure.

Yang et al. (2021) made a retrospective analysis of prospectively collected data from patients with septic shock, admitted to the Peking Union Medical College Hospital Medical Intensive Care Unit (MICU); where all received norepinephrine 0.32-1.13 mcg/kg/min (0.56). They observed the pulmonary focus (62.0%) followed by the abdomen (20.4%) as the etiology of septic shock, divided into 2 groups (weaning from ΔNE [<0 mcg/ min] and worsening of ΔNE [>1 mcg/min] according to implementation times after fluid resuscitation), observing that 57.4% of the patients were responders to preload (fluids) compared to 42.6% who were responders to vasopressors, and only 25.9% of all were responders to both fluids and vasopressors, concluding that the assessment of arterial load using effective arterial elastance in patients with septic shock may help clinicians to detect patients in for which it is possible to initiate weaning from norepinephrine in the early phase of resuscitation.

Discussion

Septic shock is defined as the subset of sepsis that includes underlying circulatory, cellular, and metabolic abnormalities, through which the cardiovascular system is unable to maintain an adequate supply of O2 in the tissues to meet the demand (Caballer et al, 2022); its clinical definition is sepsis associated with persistent hypotension, which requires the use of vasopressors to maintain a MAP>65 mmHg, in addition to serum lactate levels greater than 18 mg/dL or >2 mmol/L despite adequate volume resuscitation, that is, after volume resuscitation, not at the time of shock recognition (Ko et al, 2018).

Constituting to date a syndrome with high mortality (up to 50% in developed countries), identifying microvascular alterations in septic patients (the main ones being endothelial dysfunction and vascular hyporeactivity), in which a correction of systemic hemodynamics has been achieved, relating its severity to the results (Menezes et al, 2018; Caballer et al, 2022).

In patients with severe sepsis, their monitoring should be prioritized. In the event of having hemodynamic monitoring devices, their insertion should be prioritized, as well as the insertion of central venous accesses, since they allow evaluation of cardiac output and administration of drugs also allow better control and measurement of oxygenation and heart rate. Vasopressor administration should not be delayed due to lack of central venous access or invasive monitoring, with norepinephrine (since it stimulates α1-adrenergic receptors) being preferred as the first-line agent followed by vasopressin in refractory shock or epinephrine as a second-line agent. However, remembering that no superiority has been observed in terms of survival of patients treated with epinephrine alone compared to those treated with a combination of NE and dobutamine. Even though the ANDROMEDA-SHOCK study did not reach statistical significance ($p = 0.06$), the capillary refill time-guided strategy was associated with lower 28-day mortality, which has recently been confirmed by several post-hoc treatment analyses. Antimicrobial therapy is also a pillar of septic shock therapy in conjunction with fluid resuscitation. Its establishment should be prioritized within the first two hours, and as far as possible and according to the resources of the institutions after taking blood culture samples, starting with a loading dose greater than 1.5 times the standard dose; however, to optimize the efficacy of antimicrobial therapy, the pharmacokinetic/pharmacodynamic indices of each class of antibiotic should be considered, especially for maintenance doses (shortened dose intervals or continuous infusions, among others), since they can be affected by volumetric expansion and the consequent hypoalbuminemia or increased capillary permeability (Gavelli et al, 2021).

In patients with evidence of pre-existing heart failure and intercurrence with septic shock, special care must be taken in fluid resuscitation, since fluid boluses (30 mL/kg)

can lead to fluid overload, with consequent acute pulmonary edema and need for mechanical ventilation, which increases mortality in these patients. Current heart failure recommendations promote strategies to reduce ventricular afterload (to improve CO and reduce myocardial oxygen demand) and optimize cardiac preload (increasing CO without affecting myocardial oxygen demand). It should be remembered that these patients they may have a mixed form of cardiogenic and septic shock (attributable to sepsis-induced myocardial dysfunction or hypoperfusion); even when it has not been adequately evidenced, the lactate level should be monitored to maintain adequate oxygenation, values greater than 2 mmol/L are indicative of hypoxemia due to septic shock, either due to hypoperfusion or adrenergic overstimulation (β-2 agonism) by catecholamines endogenous or exogenous epinephrine, as well as the capillary refill time which is prolonged by heart failure in patients with low cardiac output (Jones et al, 2021).

To achieve adequate resuscitation, it is proposed to administer crystalloids (which, 60 minutes after infusion, only 20% of the volume remains in the intravascular space) at a rate of 30 ml/kg of ideal weight intravenously in the first 3 hours of initial fluid resuscitation. Being able to use static indices such as determination of RV preload through CVP, LV is preload by measuring pulmonary artery occlusion pressure (PAOP), transpulmonary thermodilution, through hemodynamic monitoring or measurement of end-diastolic volumes using echocardiography, as well as the delta CO2 (CO2 gap: PVCO2-PACO2), which allows guidance towards low cardiac output with values greater than 6 mmHG (del Río-Carbajo et al, 2022; Caballer et al, 2022; Gavelli et al, 2021). Even though there is a broad consensus on the preference for crystalloids over colloids in initial resuscitation, the SAFE trial showed lower mortality in those treated with 4% albumin in septic patients (Borges et al, 2022).

Emphasis should be placed on the fact that antibiotic therapy is a fundamental pillar in sepsis, and adequate treatment is important, molecular identification techniques allow an accelerated diagnosis, and optimize the management of antimicrobials. Among these tools are FILM-Array (even when the evidence is of moderate quality in terms of sensitivity and specificity, and low-quality evidence that its use produces clinical benefits on mortality or health services when used in patients with suspected sepsis and positive blood cultures) and MALDI-TOF (Rodrigues et al, 2016).

However, the use of empirical schemes serves to reduce mortality and it is recommended that they be established as soon as possible based not only on fever (which is only of infectious etiology in 50% of cases of patients with shock), nor on the presence of SIRS (6,29,30). Extracorporeal membrane oxygenation has reported high mortality rates (>80%), with disappointing results (del Río-Carbajo et al, 2022).

Conclusions

Management of septic shock should be guided by goals such as maintaining a MAP >65 mmHg, serum lactate <2 mmol/L, capillary refill <3 seconds, and ΔCO2 <6 mmHg, as these can be used as markers of hypoperfusion and inadequate cardiac output. To achieve these goals, fluid resuscitation with crystalloids should be started promptly in conjunction with antibiotic therapy in the first two hours (taking culture samples before exposure to antibiotics and, to the extent possible, using phenotypic identification methods such as MALDI-TOF, which accelerate the delivery of results) with a recommended loading dose of 1.5 times more than usual followed by maintenance adjusted to PK/PD. The use of vasopressors (NE as the first therapeutic line, which can be associated with vasopressin in refractory shock or dobutamine in the case of coexisting septic shock) will allow the objectives to be met, improving the outcomes for patients.

Authors' contributions

Conceptualization: GGFC; Data curation: GGFC and SGVR; Formal analysis: GGFC and SGVR; Investigation: GGFC; Methodology: GGFC; Project administration: GGFC; Resources: GGFC and SGVR; Supervision: SGVR; Validation: SGVR; Writing-original draft preparation: GGFC and SGVR; Writing-review and editing: SGVR.

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Conflict of interest

There is no conflict of interest was reported by the authors.

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